

***Remarks***

***Support for the Amendments Status of the Claims***

Claims 1-16, 93-101, 106-107, 112-133, 138-159, 162, 164-165, 167, 169, 171, 173-175, 177, 181-186, 188, 193-195, 199 and 200 are pending in the application, with claim 1 being the sole independent claim. Claims 194 and 195 have been amended. Claims 199 and 200 are new. Claims 12-16, 93-101, 106-107, 112-133, 138-140, 142-154, 162, 165, 167, 171, 175, 196-195 have been withdrawn from prosecution. Claims 196 and 197 have been canceled without prejudice to or disclaimer of the subject matter therein. Applicants reserve the right to pursue any of the canceled subject matter in related applications. Collectively, claims 17-92, 102-105, 108-111, 134-137, 160-161, 163, 166, 168, 170, 172, 176, 178-180, 187, 189-192, and 196-198 have been canceled without prejudice. Support for the amendments to the claims and new claims can be found throughout the specification as originally filed, for example, at page 27, lines 32-34 and page 34, line 23 to page 35, line 4. These changes are believed to introduce no new matter.

***Rejection Under 35 U.S.C. § 112, First Paragraph, Written Description***

The Examiner has maintained the rejection of claims 1-11, 141, 164, 169, 173, 174, 177, 181-186, 188, 193-195 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement. In particular, the Examiner has alleged that the detailed description in the specification “describes the 122 kinase genes specifically from the yeast genome, not the broad claimed any kinase from any type of mammals or Drosophila or functional domains thereof. A written description of

a single species would not be a written description for the genus as claimed.” Office Action at pages 4-5. Moreover, in response to Applicants' arguments on the record that protein kinases and their functional kinase domains were generally known to have a well conserved correlation between structure and function and thus, were readily identified, expressed and assayed for kinase activity, the Examiner has asserted that “the claims are not drawn only to the alleged known, well characterized kinases from yeast, mammals and *Drosophila* or functional domain thereof. Rather, to a kinase array for all or any kind of kinase from e.g., mammals or functional domain immobilized in every conceivable manner on any kind of solid support.” Office Action at pages 7-8. Additionally, while acknowledging that the level of skill and knowledge in the art was high, the Examiner has alleged that there was also high unpredictability in the “gene art” for making arrays containing proteins, such as protein kinases. Office Action at pages 9-10.

Applicants respectfully disagree with and traverse this rejection.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 U.S.P.Q.2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the

claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient. See *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997). M.P.E.P. § 2163.

The Federal Circuit has recently re-emphasized the well-settled principle of law that “[t]he written description requirement does not require the applicant ‘to describe exactly the subject matter claimed, [instead] the description must clearly allow persons of ordinary skill in the art to recognize that [they] invented what is claimed,’” *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000) (“*Unocal*”). The Court in *Unocal* emphasized the importance of what the person of ordinary skill in the art would understand from reading the specification, rather than whether the specific embodiments had been explicitly described or exemplified. The Federal Circuit has recently reaffirmed that the written description requirement must be viewed in light of the state of the art at the time of filing. *Capon v. Eshhar*, 418 F.3d 1349, 1357-1358 (Fed Cir. 2005) (“[t]he descriptive text needed to meet these [written description] requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence.”). Moreover, in *Capon*, the Federal Circuit stated that the Board's reliance on *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997), *Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993), *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 927 F.2d 1200 (Fed. Cir. 1991) and *Enzo Biochem Inc., v. GenProbe, Inc.*, 296 F.3d 1316 (Fed. Cir. 2002), for the case at bar was incorrect and explained that “[n]one of the cases to which the Board attributes the requirement of total DNA re-analysis, i.e., *Regents v. Lilly*, *Fiers v. Revel*, *Amgen* [v.

*Chugai], or Enzo Biochem, require a re-description of what was already known." Id.*  
(emphases added).

Applicants respectfully submit that for at least the reasons of record and those that follow, the claims fully satisfy the statutory requirements for written description. More particularly, the specification provides extensive disclosure relating to the production and use of positionally addressable arrays containing purified active protein kinases (and fragments containing functional kinase domains) from yeast and other organisms, including mammals and *Drosophila*. See, e.g., specification at page 11, lines 14-25. The specification additionally discloses working examples demonstrating the production of positionally addressable protein arrays containing 111 distinct purified active yeast protein kinases that represent approximately 93% of the protein kinases encoded by the yeast genome. See, e.g., Example 1, page 27, line 19 to page 38, line 7. The specification also discloses that these working examples are intended to be exemplary and non-limiting. See, e.g., specification at page 46, lines 19-22.

As acknowledged by the Examiner, the level of skill in the art on the priority date of the application was high. Office Action at page 9. Similarly, the knowledge in the art of proteomics relating to protein kinases was also high. In particular, members of the protein kinase family were known to contain a highly conserved catalytic kinase domain that had an art-recognized correlation between primary amino acid sequence (i.e., structure) and kinase activity (i.e., function). See, e.g., Hunter and Plowman, *TIBS* 22:18-22 (1997) at page 18, first column, first paragraph (cited in Applicants' 6<sup>th</sup> SIDS submitted on April 20, 2009). Moreover, as testified in the Supplemental Declaration of Barry Schweitzer, Ph.D. ("Supplemental Schweitzer Declaration"; filed herewith),

"protein kinases were and could be, reliably recognized and distinguished based on the sequence of their kinase domain." Supplemental Schweitzer Declaration, ¶9.

In view of the high level of skill and knowledge in the art relating to protein kinases and the extensive disclosure in the specification relating to the production and use of positionally addressable arrays containing purified active protein kinases (and fragments containing functional kinase domains) from yeast and other organisms, a person of ordinary skill in the art, reading the application, would have reasonably concluded that the inventors were in possession of the claimed positionally addressable protein arrays. This position is further supported by Dr. Schweitzer's testimony:

a scientist of ordinary skill, enlightened by the disclosure and teaching of the '781 application, would have readily understood that the disclosure and teaching in the application applies to the production of equally successful arrays containing active protein kinases from other organisms (e.g., a *Drosophila* or a mammal) that could readily be recognized and distinguished from other proteins and that could be arrayed as active proteins according to the methods and techniques disclosed in the '781 application, irrespective of whether the arrayed kinases were well characterized or uncharacterized, or whether the kinases were then known or yet to be recognized. For at least these reasons, it is my opinion that a scientist of ordinary skill in the field of proteomics on May 4, 2001, reading the '781 application, would have reasonably concluded that the application amply describes the claimed arrays which contain at least 61 purified active kinases (and fragments containing a functional kinase domain) of a yeast, a *Drosophila* or a mammal (e.g., a human).

Supplemental Schweitzer Declaration, ¶12. See also *Id.*, ¶¶s 17 and 29-31.

Accordingly, Applicants respectfully submit that the claims fully satisfy the written description requirement.

On pages 4-5 of the Office Action, the Examiner has alleged that the disclosure in the specification of "a single species" represented by the arraying of 122 yeast kinases does not provide an adequate written description of the claimed genus of protein arrays.

In response, Applicants point out that the specification discloses working examples demonstrating the use of disclosed methods and techniques to produce and screen 17 positionally addressable arrays that each contain 111 purified active protein kinases corresponding to a diverse collection of kinases that in turn, collectively represent more than 90% of all the protein kinases in a single organism (i.e., yeast). As attested by Dr. Schweitzer, the disclosure of the specification provides "compelling" support that the methods and techniques disclosed in the application could be applied to routinely and predictably produce arrays containing at least 61 active protein kinases (and fragments containing a functional kinase domain) from an organism, such as a yeast, a *Drosophila*, or a mammal." Supplemental Schweitzer Declaration, ¶13. Dr. Schweitzer further testifies:

the disclosure in Example 1 of the production and use of 17 arrays that each display 111 active yeast protein provides further support that would lead a scientist of ordinary skill in the field of proteomics to reasonably conclude that the techniques and methodology described in the '781 application are reproducible, generally applicable to actively arraying large numbers of active diverse protein kinases on a single array, and can be routinely used or adapted to produce and use arrays containing at least 61 active protein kinases (and fragments containing a functional kinase domain) from, for example, a yeast, a human or another mammal, or a *Drosophila*.

Supplemental Schweitzer Declaration, ¶13.

On pages 9-10 of the Office Action, the Examiner has asserted that there was high unpredictability in the "gene art" for making arrays containing proteins such as, protein kinases. The Examiner has acknowledged the detailed description of the yeast kinase array disclosed in Example 1, but alleges that the specification does not adequately describe the array of "any type of mammal kinase and/or *Drosophila*." Office Action at page 10. In particular, the Examiner has alleged that the specification "does

not describe that the 61 kinase present in yeast can be extrapolated or are similarly present to the different numbers and kinds of kinases found in any kind of mammals or *Drosophila*." Office Action at page 10.

In response, Applicants respectfully disagree and submit that the position taken by the Examiner disregards how a person of ordinary skill in the art would have understood the substantial teaching of the specification that includes disclosure of the successful arraying of large numbers of diverse, purified and active protein kinase family members. Applicants submit that when properly placed in the context of the knowledge and skill in the art, a person of ordinary skill in the art, enlightened by the specification would have reasonably concluded that the disclosed methods and techniques would be generally applicable to making and using positionally addressable protein kinase arrays containing purified active protein kinases from organisms other than yeast, and that the Applicants were in possession of the claimed arrays on the priority date. This position is further supported in Dr. Schweitzer's testimony:

while I agree that producing protein arrays might generally be viewed as challenging, particularly, when compared to producing DNA microarrays, I *disagree* that this viewpoint would have prevented a scientist of ordinary skill in art of proteomics on May 4, 2001, enlightened by the disclosure and guidance provided by the '781 application, from reasonably concluding that the '781 application adequately describes the making and using of protein arrays containing at least 61 active protein kinases from yeast or another organism, including a *Drosophila* or a mammal, such as a human (including fragments having a functional kinase domain of these protein kinases). In particular, the high percentage (i.e., greater than 90%) of the large number of distinct protein kinases that are active on the arrays disclosed in Example 1 (i.e., 111) indicates that protein stability, choice of immobilization technique and non-specific binding did not prevent the successful arraying and use of protein kinase arrays prepared according to the disclosure and teaching of the '781 application. Furthermore, in view of the known correlation between the primary sequence and activity of the kinase domain and the general applicability of the methods disclosed and taught in the '781 application for recombinantly expressing, purifying, and

arraying a large number of distinct and diverse active protein kinases from other organisms, a scientist of ordinary skill in the field of proteomics would have reasonably expected that the methods, techniques and reagents disclosed in the '781 application could be used to produce equally successful arrays containing at least 61 purified active protein kinases (or fragments containing a functional kinase domain) of yeast or another organism, such as a *Drosophila* or a mammal (e.g., a human).

Supplemental Schweitzer Declaration, ¶17 (emphasis in original). See also *Id.*, ¶¶s 14-16.

In view of the foregoing remarks, and those of record, Applicants respectfully submit that the claims fully satisfy the written description requirement and respectfully request reconsideration and withdrawal of this rejection.

***Rejection Under 35 U.S.C. § 112, First Paragraph, Enablement***

The Examiner has maintained the rejection of claims 1-11, 141, 164, 169, 173, 174, 177, 181-186, 188 and 193-195 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the enablement requirement. Office Action at pages 11-20. More particularly, the Examiner has acknowledged that the specification provides an enabling disclosure for arrays containing Ser/Thr and Tyr kinases from yeast, but alleges that the specification "does not reasonably provide enablement for the broad scope of an array of 61 kinases and functional domain kinase from an organism [sic.] as mammal, yeast or *Drosophila*." Office Action at page 11. The Examiner further asserts that the claimed arrays encompass a broad genus of compositions that include any members of protein kinases from mammals, yeast and *Drosophila* and that the claim scope does not place any limitations on the kind, number and/or length of the kinases. Office Action at pages 11-12. Furthermore, the Examiner has alleged that the specification does not provide any

reasonable assurance that the 61 kinases found in yeast could be found in mammals or *Drosophila*, and made into an array. Office Action at page 12. The Examiner has also asserted that in a highly unpredictable art, such as biotechnology, one cannot predict from a single species its correspondence or extrapolation to a genus, and then concluded that the claimed protein arrays are not enabled. Office Action at pages 12-13.

Applicants respectfully disagree with and traverse this rejection and submit that for at least the reasons on the record and those that follow, the claims are fully enabled.

The test for enablement is whether "one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). As set forth in M.P.E.P. § 2164.01(a), factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue" include the breadth of the claims; the nature of the invention; the state of the prior art; the level of one of ordinary skill; the level of predictability in the art; the amount of direction provided by the inventor; the existence of working examples; and the quantity of experimentation needed to make or use the invention based on the content of the disclosure. See *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). According to the Federal Circuit, "a considerable amount of experimentation is permissible, if it is merely routine" *In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Jackson*, 217 U.S.P.Q. 804 (Board of Patent Appeals and Interferences, 1982).

As discussed above, the specification provides extensive disclosure and teaching relating to manufacture and use of the claimed positionally addressable protein arrays. For example, the specification discloses the recombinant production of protein kinase fusion proteins containing a tag (e.g., glutathione-S-transferase (GST)); the recombinant expression and purification of tagged protein kinase fusion proteins corresponding to almost every protein kinase in the kinome of an organism (i.e., *Saccharomyces cerevisiae*); the use of reagents having affinity for the tag component (e.g., glutathione) to rapidly purify these tagged kinase fusion proteins under non-denaturing conditions; the design, manufacture and optimization of solid supports and linking agents; the immobilization and arraying of the tagged kinase fusion proteins onto the solid support in a manner such that the arrayed proteins retain kinase activity; and the subsequent assaying of the arrayed protein kinases for kinase activity. See e.g., specification at page 26, line 25 to page 37, line 34. In Example 1, the specification teaches and describes the production of 17 exemplary arrays that each contain 111 distinct purified active yeast protein kinases collectively representing most of the protein kinases in *Saccharomyces cerevisiae*. Significantly, more than 90% of the proteins arrayed in Example 1 display kinase activity. See, e.g., specification at page 33, lines 14-15 and page 28, lines 12-14.

As discussed above, there was a high level of skill and knowledge in the art on the priority date of the application and there was an art-recognized correlation between the primary sequence (i.e., structure) and kinase activity (i.e., function) of the catalytic kinase domain of protein kinases. Kinase domains were known to represent discreet regions containing characteristic patterns of conserved and invariant or nearly invariant amino acid residues that play essential roles in conferring kinase activity. Moreover

persons of ordinary skill in the art relied on the known correlation between structure and kinase function to reliably recognize and distinguish protein kinases based on their primary sequences. Numerous activity studies had validated the use of sequence analysis to identify protein kinases. See, e.g., Supplemental Schweitzer Declaration, ¶18. The reliability of this sequence based approach for identifying protein kinases is further corroborated by the demonstration in Example 1 of the specification that almost every yeast ORF predicted by Hunter and Plowman to encode a protein kinase based on primary sequence analysis did indeed encode a protein that displays kinase activity when produced and arrayed according to the teaching and methods disclosed in the specification. See e.g., specification at page 27, line 23 to page 28, line 22; and page 38, lines 26-27.

Therefore, Applicants respectfully submit that a person of ordinary skill in the art would have reasonably expected that proteins containing a primary sequence corresponding to a kinases domain and fragments containing a functional kinase domain (including fully characterized protein kinases, poorly characterized protein kinases, and proteins containing kinase domains that are different from those found in yeast) would display kinase activity.

Moreover, in view of the high level of knowledge and skill in the art and the extensive disclosure and teaching of the specification (including working examples demonstrating the successful manufacture and use of arrays containing purified active proteins kinases corresponding to almost every protein kinase in the kinome of an organism), as discussed herein and on the record, a scientist of ordinary skill in the art, enlightened by the disclosure and teaching of the specification would have reasonably

concluded that the methods and techniques disclosed in the specification could be routinely applied or modified to make and use arrays containing at least 61 purified active protein kinases (or fragments containing functional kinase domains), from yeast, *Drosophila*, or a mammal (e.g., a human), without having to undertake undue experimentation.

Applicants' position is further supported by the testimony of Dr. Schweitzer wherein after reviewing the state and level of skill of the art and the disclosure of the specification, he concludes,

[i]n view of the extensive disclosure, teaching and guidance of the '781 application and the high level of knowledge and skill in the field of proteomics on May 4, 2001, a scientist of ordinary skill, having read the '781 application, would have reasonably concluded that the disclosure and teaching of the '781 application could be routinely applied or modified to produce arrays containing at least 61 purified active protein kinases (including fragments having a functional kinase domain) from an organism, such as from a mammal, a yeast, or a *Drosophila*. Moreover, in view of the disclosure and teaching of the '781 application, a scientist of ordinary skill would have reasonably come to this same conclusions irrespective of whether the arrayed protein kinases are: (a) from a yeast, a *Drosophila*, or from a human or any other mammal; (b) fully characterized, poorly characterized; or yet to be identified; or (c) full-length, a fragment containing a functional kinase domain, or a polypeptide predicted to have protein kinase activity based on its deduced amino acid sequence.

Supplemental Schweitzer Declaration, ¶20. See also *Id.*, ¶¶s 32-33.

As in the written description rejection, the Examiner contends that the field of biotechnology and particularly protein arraying is unpredictable and that consequently one cannot determine whether the generation of arrays comprising kinases of one organism (yeast) would be predictive of arrays comprising kinases of other organisms such as, mammals or *Drosophila*. For example, on pages 12-13 of the Office Action, the

Examiner makes the sweeping generalization that "[f]actors such as the compatibility of the array with the substrate and compounds disposed therein, the compounds (kinases) itself and other unpredictable variables can affect the active form of any kinase. Thus, one cannot predict from a single species its correspondence or extrapolation to the genus as claimed."

Applicants respectfully disagree and submit that in view of the high level of knowledge and skill in the art, person of ordinary skill in the art, enlightened by the extensive disclosure of the specification would reasonably expect that the methods and teachings of the specification would be equally applicable to making and using the claimed positionally addressable arrays containing purified active protein kinases from organisms other than yeast, including *Drosophila* and mammals, such as humans. This position is supported by Dr. Schweitzer's testimony:

as would be immediately apparent to a scientist of ordinary skill in the field of proteomics on May 4, 2001, substrate and array compatibility, distinctions between kinases, and "other unpredictable variables" did *not* prevent the successful arraying of the purified active yeast protein kinases using the methods and techniques disclosed in the '781 application. Moreover, in my opinion, the Patent Office has provided no reasonable or compelling basis that would have led a scientist of ordinary skill in the field of proteomics on May 4, 2001, enlightened by the disclosure and teaching of the '781 application, to disregard or doubt that the generally applicable disclosure and teachings of the '781 application could be equally successfully applied to array purified active protein kinases from yeast or from other organisms such as a *Drosophila*, or a mammal.

Supplemental Schweitzer Declaration, ¶23.

Moreover, Applicants submit that a person of ordinary skill in the art, enlightened by the disclosure of the specification would have reasonably concluded that nothing more than routine experimentation was required to make and use the full scope of the

claimed positionally addressable protein arrays. This position is finds support in the arguments and testimony presented herein and on the record, including Dr. Schweitzer's testimony:

[a]s would be immediately apparent to a scientist of ordinary skill, the use of the approaches disclosed in the '781 application for recombinantly expressing and purifying tagged protein kinases using affinity reagents would be expected to be generally applicable to recombinantly expressing, purifying, and arraying protein kinases from any organism. Moreover, I disagree with the Patent Office and in my opinion, a scientist of ordinary skill, reading the disclosure of the '781 application, particularly Example 1, would have reasonably concluded that the disclosed methods and techniques for producing and arraying large numbers of active purified protein kinases, including for example, methods and techniques for recombinantly producing, purifying and arraying active protein kinases, would be expected to be equally applicable to, and would require at most routine modification for, successfully producing arrays containing active purified protein kinases from yeast and other organisms, including for example, a mammal (e.g., a human), or a *Drosophila*.

Supplemental Schweitzer Declaration, ¶23, see also *Id.*, ¶¶s 24-28 and 32-33.

On page 20 of the Office Action, the Examiner refers to the first Schweitzer Declaration, dated March 2, 2010, and alleges that "Schweitzer has not extrapolated or predicted its findings to any other family o [sic.] human protein kinases which consist of more than 500 members to which only a fraction has been characterized to date." In response to this allegation, Dr. Schweitzer testifies:

[t]o directly address the point raised by the Patent Office, it is my opinion that a scientist of ordinary skill, having read the '781 application on May 4, 2001, would have reasonably expected that by applying the disclosure and teaching of the '781 application, well characterized, poorly characterized, and uncharacterized protein kinases could be routinely and successfully arrayed as active kinases. Moreover, on May 4, 2001, a scientist of ordinary skill in the field of proteomics would indeed have reasonably expected that by applying the disclosure and teaching of the '781 application, at least 61 protein kinases could similarly be routinely and

successfully arrayed and thus, would likewise display the requisite protein kinase activity, irrespective of whether the kinases are: (a) known or yet to be discovered; (b) well characterized, poorly characterized or uncharacterized; (c) full-length or a fragment containing a kinase domain, or (d) from a yeast, a *Drosophila*, or a human or another mammal.

Supplemental Schweitzer Declaration, ¶28.

In summary, the present application presents a situation very similar to in *In re Wands* where the specification was found enabling for the claimed antibodies because of the considerable direction and guidance in the specification, the high level of skill in the art, and the well-established methods needed to practice the invention. The present specification, like *In re Wands*, provides more than ample guidance to those of ordinary skill in the art for how to make and use the claimed positionally addressable arrays.

For at least the above reasons and those of record, Applicants respectfully submit that the claims are fully enabled and respectfully request that this rejection be reconsidered and withdrawn.

***Rejection Under 35 U.S.C. § 102(a), or 35 U.S.C. § 103(a), Over Uetz***

The Examiner has maintained the rejection of claims 1-11, 141, 181-186, 188 and 193-195, as allegedly being anticipated by, or in the alternative, as allegedly obvious in view of, Uetz *et al.*, *Nature* 403:623-631 (2000) (hereinafter "Uetz"). More particularly, the Examiner has asserted that Uetz disclose 96 well arrays containing yeast genome encoded proteins and has alleged that the kinases contained on the claimed array were either inherently contained on the arrays of Uetz or would have been obvious to determine given the identified genome of yeast as taught in Uetz. Office Action at pages 20-26.

Applicants respectfully disagree with and traverse these rejections.

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California* 814 F.2d 628, 2 U.S.P.Q.2d 1051 (Fed. Cir. 1987); M.P.E.P. § 2131.

The pending claims are directed to positionally addressable arrays that comprise a plurality of different substances on a solid support, *with each different substance being at a different position on the solid support*, wherein the density of the different substances at the different positions on the solid support is *at least 100 different substances per cm<sup>2</sup>*, and wherein the plurality of different substances comprises *at least 61 purified active kinases or functional kinase domains thereof* of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified active kinases or functional kinase domains thereof of a *Drosophila*.

Uetz disclose yeast two-hybrid screens in which pools of 2 distinct yeast transformants are arrayed on 96 well plates having well densities that are significantly less than the claimed positionally addressable arrays on which purified protein are arrayed at different positions at a density of 100 different positions per cubic centimeter. Accordingly, for this reason alone, Uetz do not disclose each and every element of, and therefore cannot anticipate, the claimed positionally addressable arrays.

Additionally, each "array element" disclosed in Uetz corresponds to a pool containing two different yeast clones (i.e., "living transformants") transformed with vectors containing a predicted *Saccharomyces cerevisiae* ORF sequence encoding one of the approximately 6,000 proteins that are endogenously (and typically constitutively)

expressed by the very same host organism (i.e., *Saccharomyces cerevisiae*). Consequently, each "array element" in Uetz (that presumably corresponds to a "different position" on the claimed arrays) represents a pool of living organisms and a diverse mixture of proteins that include the two recombinant proteins (corresponding to endogenous *Saccharomyces cerevisiae* proteins) and most of the 6,000 proteins (including protein kinases) that are endogenously and constitutively expressed by *Saccharomyces cerevisiae*. Therefore, Uetz cannot reasonably be interpreted to disclose an array containing any purified proteins, let alone purified active kinases, as recited in the claims. Accordingly, Uetz do not disclose each and every element as set forth in the claimed positionally addressable arrays and cannot anticipate the claims.

On pages 22-23 of the Office Action, the Examiner relies on a passing reference made in Uetz to support the allegation that Uetz disclose anticipatory protein arrays containing purified proteins. In response, Applicants point out that this relied upon passing reference amounts to nothing more than a general statement that an alternative type of protein array from the living transformant arrays described in Uetz is "composed solely of purified proteins." Uetz paragraph spanning cols 1 and 2. Moreover, the Examiner's reliance on this disclosure is misplaced and Applicants point out that in particular: (a) contrary to the position taken by the Examiner, the cited disclosure indicates that the authors of Uetz do not themselves believe that the transformed yeast arrays disclosed in Uetz contain "purified" proteins; and (b) the passing reference in Uetz regarding alternative protein arraying formats provides no disclosure or guidance relating to the type, number, activity, or density of the "purified" proteins that "may be envisioned" on this alternatively formatted array.

Applicants also point out that claims 164, 165, 169, 173, 174, and 177 recite arrays containing protein kinases from mammals. Uetz do not disclose arrays containing functional kinases or functional kinase domains of *mammals*, such as mice, rats and humans, and therefore, cannot anticipate claims 164, 165, 169, 173, 174, and 177.

In view of the above comments and those of record, Applicants respectfully submit that Uetz do not anticipate the claims and respectfully request that this aspect of the rejection be reconsidered and withdrawn.

Moreover, the claimed positionally addressable arrays are nonobvious in view of Uetz.

The factors relating to obviousness that are to be considered under 35 U.S.C. § 103(a), are the scope and content of the prior art; the differences between the prior art and the claims at issue; and the level of ordinary skill in the pertinent art. *See Graham v. John Deere*, 86 S.Ct. 684 (1966) and M.P.E.P. §2141. This analysis has been the standard for 40 years, and remains the law today. *See KSR International Co v. Teleflex Inc.*, 550 U.S. 398; 82 U.S.P.Q.2d at 1385 (2007). The Office has recently published Examination Guidelines to aid Examiners in formulating obviousness rejections. *See Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 in view of the Supreme Court decision in KSR International v. Teleflex Inc.* Fed. Reg. Vol. 72, pp. 57526 to 57535 (October 10, 2007), hereinafter "the Examination Guidelines." Seven rationales are suggested by which obviousness may be found, *e.g.*, by combining elements in the art or substituting one known element for another. As a common thread through all the rationales, the Examiner must establish on the record that a person of ordinary skill in the art would have recognized that the results of the combination or

substitution were *predictable*. *Id.*, *e.g.*, at 57529. In particular "[w]hen the prior art teaches away from combining certain known elements, discovery of successful means of combining them is more likely to be nonobvious." *KSR*, 550 U.S. at 416, 82 U.S.P.Q.2d at 1395.

Applicants submit that for at least the reasons of record and those that follow, a person of ordinary skill in the art, reading Uetz would not have predictably arrived at the claimed positionally addressable arrays comprising a plurality of different substances on a solid support, with each different substance being at a different position on the solid support, wherein the density of the different substances on the solid support is at least 100 different substances per cm<sup>2</sup>, and wherein the plurality of different substances comprises at least 61 purified active kinases or functional kinase domains thereof of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified active kinases or functional kinase domains thereof of a *Drosophila*.

The teaching and arrays of Uetz are substantially distinct from the claimed positionally addressable arrays. Uetz teach a large scale yeast two-hybrid screen assay touted as being "simple, sensitive, and amenable to high-throughput methods." Uetz, page 623, col. 1, first paragraph. As discussed above, the large scale assay of Uetz involves an array at which each position on the array contains a pool of "*living transformants*" that express unpurified mixtures containing two different recombinant proteins (corresponding to proteins endogenously expressed by the host cell) and most of the 6,000 other proteins such as, protein kinases, that are constitutively expressed by the host cell.

Uetz teach a transformed yeast host cell array expressed on 96 well plates that is useful for analyzing protein-protein interactions *in vivo* in yeast cells using a two hybrid screen. Uetz do not teach positionally addressable arrays comprising a plurality of different substances on a solid support, *with each different substance being at a different position on the solid support*, wherein the density of the different substances on the solid support is *at least 100 different substances per cm<sup>2</sup>*, and wherein the plurality of different substances comprises *at least 61 purified active kinases or functional kinase domains thereof* of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified active kinases or functional kinase domains thereof of a Drosophila.

In view of the teaching of Uetz, a person of ordinary skill in the art would not have had a reason to modify the teaching of Uetz to arrive at the claimed array. For example, one skilled in the art would not have a reason to purify and immobilize proteins produced in Uetz because to do so undermines the entire rationale of using the two hybrid assay to detect protein-protein interactions through *in vivo* transcription initiation and the expression of a reporter gene.

In addition, even if, *arguendo*, a person of ordinary skill in the art had reason to modify the teaching of Uetz, they would not have predictably arrived at the claimed positionally addressable arrays comprising a plurality of different substances on a solid support, *with each different substance being at a different position on the solid support*, wherein the density of the different substances on the solid support is *at least 100 different substances per cm<sup>2</sup>*, and wherein the plurality of different substances comprises *at least 61 purified active kinases or functional kinase domains thereof* of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified

active kinases or functional kinase domains thereof of a *Drosophila*. Furthermore, the passing reference in Uetz to arrays containing purified proteins that is discussed above is unaccompanied by any disclosure or guidance relating to the type, number, activity, or density of the "purified" proteins that "may be envisioned" on this alternatively formatted array. Most significantly, the disclosure of Uetz does not enable arrays containing arrayed purified active proteins. Therefore, even if a person of ordinary skill in the art were motivated to modify the teaching of Uetz, they would not have reasonably expected to be able to successfully make and use the claimed positionally addressable protein arrays.

Accordingly Applicants submit that the claimed positionally addressable arrays are non-obvious in view of Uetz and respectfully request that this rejection be reconsidered and withdrawn.

In view of the foregoing remarks, Applicants respectfully submit that the claims are novel and non-obvious over Uetz and respectfully request that the rejections be reconsidered and withdrawn.

***Rejection Under 35 U.S.C. § 103(a) over Shalon, in view of Felder or Lafferty***

The rejection of claims 1-11, 141, 181-186, 188 and 193-195 under 35 U.S.C. § 103(a), as allegedly being unpatentable over Shalon (WO 95/35505; hereinafter "Shalon") in view Felder *et al.* (U.S. Patent No. 6,458,533; hereinafter "Felder") or Lafferty (U.S. Patent No. 6,972,183; hereinafter "Lafferty") has been maintained.

More particularly, the Examiner maintains that Shalon disclose a microarray having regions with a density of at least about  $100/\text{cm}^2$ , and that the arrays can comprise enzymes. The Examiner acknowledges however, that Shalon do not disclose arrays comprising kinases. The Examiner relies on the disclosures of Felder or Lafferty to cure this deficiency. Specifically, the Examiner alleges that Felder teach that kinases are enzymes, and Lafferty disclose an array containing substrate-enzymes, such as kinases. In view of the above disclosures, the Examiner concludes that it would have been obvious to prepare the arrays disclosed in Shalon using the kinases disclosed in Felder and Lafferty, and therefore, that the claimed positionally addressable arrays are obvious.

Applicants respectfully disagree with and traverse this rejection and submit that for at least the reasons of record and those that follow, a person of ordinary skill in the art reading Shalon in view of Felder and/or Lafferty, would not have predictably arrived at the claimed positionally addressable array comprising a plurality of different substances on a solid support, with each different substance being at a different position on the solid support, wherein the density of the different substances on the solid support is at least 100 different substances per  $\text{cm}^2$ , and wherein the plurality of different substances comprises at least 61 purified active kinases or functional kinase domains thereof of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified active kinases or functional kinase domains thereof of a *Drosophila*.

Shalon is a patent application publication in which “[t]he invention relates to a method and apparatus for fabricating microarrays of biological samples for large scale screening assays, such as arrays of DNA samples to be used in DNA hybridization assays for genetic research and diagnostic application.” Shalon, page 1, Background of

the Invention. The method and apparatus of Shalon involve "dispensing a known volume of a reagent at each of a selected array position." Shalon Abstract, see also first four paragraphs of the Summary of the Invention Section on pages 5-6. The disclosure of Shalon primarily relates to polynucleotide arrays and the screening of these arrays using polynucleotide based probes (*see* Shalon Examples 1-3). In one paragraph at the end of the written description section, Shalon makes the sweeping generalization that "[i]n addition to the genetic applications listed above, arrays of whole cells, peptides, enzymes, antibodies, antigens, receptors, ligands, phospholipids, polymers, drug cogener preparations or chemical substances can be fabricated by the means described in this invention." Shalon at page 31, line 32 to page 32, line 1. Shalon do not disclose arrays containing a single purified active protein, let alone a group of purified active proteins such as, protein kinases having kinase activity. Significantly, Shalon provide no disclosure that enables the manufacture and use of, for example an "enzyme" array.

As clarified in the Office Action, the Examiner relies on Felder and Lafferty "for its disclosure of purified kinase, as claimed, not that it has to teach purifying the kinase prior to immobilization." Office Action at page 30. The Example in Felder cited by the Examiner indicates that kinases are enzymes and discloses the *prophetic* screening of *plates containing peptide substrates with solutions containing 5 proposed known kinases*. Felder, Example 18, at cols. 33-34. Significantly, Felder do not disclose or enable arrays containing arrayed purified active kinases.

Lafferty disclose arrays containing libraries of clones that express recombinant proteins, among which are listed enzymes, including kinases. See, e.g., Lafferty Field of the Invention Section and col. 4, lines 12-22. Lafferty also disclose that the recombinant

enzymes produced by clones identified in the disclosed screens "can be recovered." Lafferty at col. 18, lines 39-49. Significantly, Felder, like Shalon and Lafferty do not disclose or enable arrays containing arrayed purified active kinases.

In view of the teaching of Shalon, Felder and Lafferty, a person of ordinary skill in the art would have no reason to modify the teaching of Shalon to arrive at the claimed positionally addressable arrays. In addition, even if, *arguendo*, a person of ordinary skill in the art had reason to modify the teaching of Shalon, they would not have predictably arrived at the claimed positionally addressable array comprising a plurality of different substances on a solid support, with each different substance being at a different position on the solid support, wherein the density of the different substances on the solid support is at least 100 different substances per cm<sup>2</sup>, and wherein the plurality of different substances comprises at least 61 purified active kinases or functional kinase domains thereof of a mammal, 61 purified active kinases or functional kinase domains thereof of a yeast, or 61 purified active kinases or functional kinase domains thereof of a *Drosophila*.

Moreover, as discussed above, the collective disclosure and teaching of Shalon, Felder, and Lafferty do not enable arrays containing arrayed purified active kinases and at best, refer to an array containing enzymes in passing without any guidance as to how such arrays would be prepared or the nature or characteristics of the proteins that would be arrayed. Accordingly, even if a person of ordinary skill in the art were motivated to modify the teaching of Shalon, Felder and Lafferty, they would not have reasonably expected to be able to successfully make and use the claimed positionally addressable protein arrays.

In view of the foregoing remarks and those on the record, Applicants respectfully submit that the claims are non-obvious in view of Shalon, Felder and Lafferty and respectfully request that this rejection be reconsidered and withdrawn.

***Conclusion***

All of the stated grounds of rejection have been properly traversed, rendered moot or otherwise overcome. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn.

Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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